Chapter 8
DNA-based asymmetric catalysis: conclusions and perspective

In this chapter, the results described in this thesis are summarized in a comprehensive fashion, and overall conclusions are drawn. A tentative stereochemical model of the DNA-based catalyst is proposed on the basis of the structural and mechanistic information described in this thesis. Furthermore, the reaction scope and the synthetic applicability of DNA-based catalysts are discussed, and future prospects are given.

8.1 Introduction

The research described in this thesis was initiated by the discovery of the first example of DNA-based asymmetric catalysis.[1] The DNA-based catalysts featured copper(II) complexes that bind DNA in a non-covalent fashion, and using this first-generation catalysts enantioselectivities of up to 49% were achieved in the Diels-Alder reaction between cyclopentadiene and azachalcone (Figure 1).

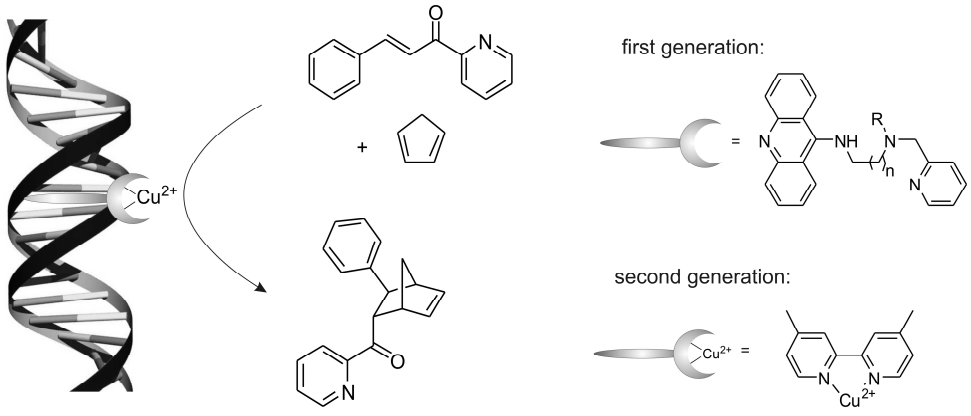

Figure 1. The concept of DNA-based asymmetric catalysis and the two generations of DNA-based catalysts.

The goal of the research described in this thesis was to develop the general concept and methodology of DNA-based asymmetric catalysis, with the aim of using this concept to discover novel reactivities, and to develop mechanistic understanding of successful catalysts.

The main achievements reported in this thesis are i) the development of a highly enantioselective DNA-based catalyst for several important C–C bond forming reactions, i.e. the Diels-Alder, Michael, and Friedel-Crafts reaction, ii) the first asymmetric *syn*-hydration of an α,β-unsaturated carbonyl compound, catalyzed by the first generation DNA-based catalysts, iii) insight into the reactivity and enantioselectivity of the highly enantioselective second-generation catalysts, and iv) insights into the structure of this catalyst.

In the present chapter, the scope and reactivity of DNA-based catalysis are discussed, and compared to biohybrid and small molecule catalysts. On the basis of the structural and mechanistic information described in this thesis a tentative structural and stereochemical model of the DNA-based catalyst is proposed. Furthermore, the synthetic applicability of DNA-based catalysts is discussed, and future prospects are given.

8.2 Reactivity of a DNA-based catalyst

DNA combined with Cu(4,4'-dimethyl-2,2'-bipyridine) (Cu-dmbpy, Figure 1) is able to induce excellent enantioselectivities upon reaction at the alkene moiety of α,β-unsaturated-2-acyl imidazoles and azachalcones. Besides cyclopentadiene, also nucleophiles were shown to react with the alkene, and the DNA induced in all cases excellent enantioselectivities (Figure 2). When dimethyl malonate and nitromethane were used as nucleophile, the corresponding Michael products were obtained, whereas the use of indole or pyrrole gave the corresponding Friedel-Crafts products. In all these cases different substituents are tolerated on the β-position of the alkene, and high ee's are generally obtained. Of these three important textbook examples of C–C bond forming reactions the Friedel-Crafts reaction is the first example of this asymmetric transformation in water as a solvent. In addition to carbon nucleophiles also water was demonstrated to react on the same conjugate position in an asymmetric fashion, indicating that DNA provides an excellent chiral environment for this combination of copper(II) complexes and substrate.

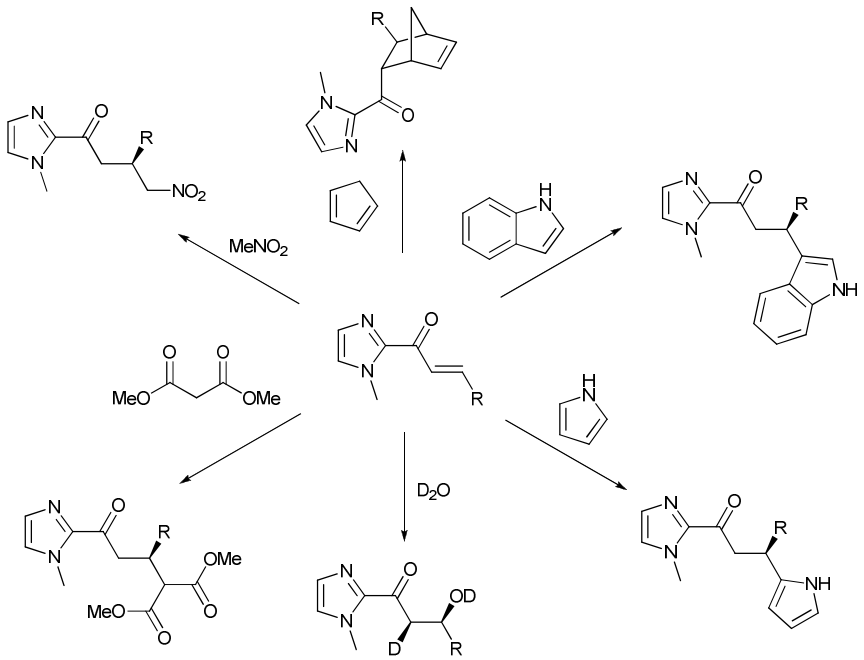

Figure 2. Reactions of α,β-unsaturated-2-acyl imidazoles catalyzed in an enantioselective fashion using a DNA-based catalyst.

The DNA has an accelerating effect on all the C–C bond forming reactions. In case of the Diels-Alder reaction the rate increase is 58-fold, in the case of the Friedel-Crafts reaction

30-fold, and it was also shown that for the Michael addition the reaction was accelerated 4-fold.[2] The reaction rate decreased due to the presence of DNA only in the case when nitromethane was employed as nucleophile.[2] For each reaction type, the rate accelerations were determined using different substrates. It was shown in chapter 5 that DNA is able to influence the affinity of the substrate to copper(II), the K_a (Figure 3), albeit that this effect was highly substrate-dependent. These differences are not large enough to fully account for the overall rate acceleration observed in these C–C bond forming reactions, and hence, the rate acceleration is mainly due to an increase in the k_{cat}. This reasoning is supported by the recent findings of Lindström et al., who showed for scandium(III)-catalyzed Michael additions in water that the binding equilibrium of the Michael donor to scandium did not affect the overall rate constant significantly when excess Michael acceptor was present,[3] which is in accord with the finding that the rate enhancement in DNA-based asymmetric catalysis is mainly due to in increase in k_{cat}. The mechanism for rate enhancement is different compared to the copper(II)-catalyzed Diels-Alder reactions in the presence of sodium dodecyl sulfate (SDS), in which the SDS accelerated the reaction by an increase in the K_a.[4]

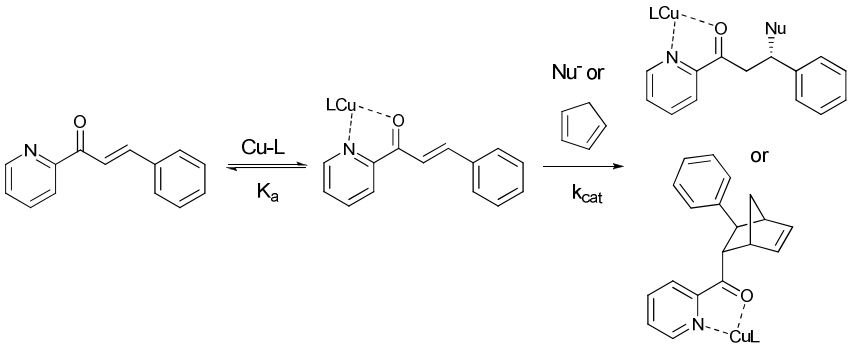

Figure 3. K_a and k_{cat} in DNA-based asymmetric catalysis.

In the Diels-Alder reaction it was shown that the enthalpy of activation is lower in the presence of DNA, and the same holds for the Friedel-Crafts reaction.[2] In these cases it was assumed that the binding of the substrate to the copper complex is independent of the temperature, which should be tested with the strong copper(II) binding azachalcone described in chapter 5 in order to obtain the most accurate values. As stated in chapter 3, an attractive explanation is that the DNA provides a chiral microenvironment which stabilizes the activated complex by shape or chemical complementarity, e.g. π-stacking interactions, increasing the rate and enantioselectivity. This explanation has also been put forward in the case of the antibody-catalyzed Diels-Alder reactions.[5] However, transition-state stabilization due to interaction with the groove can be either expressed as a decrease in enthalpy or an increase in entropy, in analogy with DNA-binding molecules.[6,7] This depends mainly on the sequence-dependent hydration, the DNA-binding mode, and the

groove-selectivity, albeit the origin of this dependence is often not known. Rate enhancement due to hydrophobic interactions is unlikely, because this is expected to lead to an increase of the entropy of activation.[8] Since rate enhancements due to the presence of DNA were also found in the case of the Friedel-Crafts and the Michael reaction, one might argue that acceleration by complementing the activated complex is not likely, since the activated complex in these reactions will have very different structures. It could be though, that the change in the structure occurring to the α,β-unsaturated ketone in the activated complex is assisted by the shape of the groove. In addition to transition state stabilization, the observation that in all cases the rate is enhanced by the DNA could also be explained by ground state destabilization of the α,β-unsaturated ketone. This could be caused by a lowering of the LUMO of the α,β-unsaturated ketone or by desolvation of the favored π-face of the α,β-unsaturated ketone. The latter explanation is attractive, since it would give rise to both a rate acceleration and an enantioselective bond formation. Finally, the enantioselectivity could be induced by the shielding the unfavoured π-face. However, it is unclear how this would result in rate acceleration; actually a deceleration would be expected as one π-face is not available for reaction anymore.

In most C–C bond forming reactions the structure provided by the G-trimer sequence induced the highest ee. The binding affinity of Cu-dmbpy to all small synthetic duplexes is similar, and hence Cu-dmbpy is distributed evenly along st-DNA. This potential limitation in the ee was overcome because the complex binding to the G-trimer accelerates the reaction most. Hence, the reaction in the presence st-DNA is dominated by the complex bound to the G-trimers, and the ee obtained is a weighted average of the sequences to which the complexes are bound. This means that selective binding of Cu-dmbpy at a well defined site on the DNA is not needed, since the catalyst bound at those locations that accelerate most dominate the reaction and determine the overall outcome. This is in contrast to other biohybrid catalysts, which require strong binding of the catalytically active cofactor to a well defined site on the biopolymer.[9-11] There are some exceptions in which the G-triplet sequence is not superior to st-DNA, which is observed in some cases of the Friedel-Crafts and the Michael reaction. Since the ee induced by st-DNA should be a weighted average of all catalysts present (chapter 3), other sequences should be responsible for the ee induced with st-DNA in these cases.

The preceding discussion holds only partially for the asymmetric conjugate addition of water for the following reasons; i) the first generation DNA-based catalysts induce the highest ee's, while in the C–C bond forming reactions the second generation induces the higher ee's, ii) the sequence selectivity of the catalytic event is different compared to the Diels-Alder reaction,[12,13] and iii) the addition occurs on the opposite π-face of the α,β-unsaturated ketone. The sequence selectivity does imply that the ee obtained in the water addition product with salmon testes DNA is an average of all the domains formed by the copper complex with the DNA. A kinetic study would give more insights on the effect of the DNA on the reaction rate. Since the opposite enantiomer compared to the C–C bond

forming reactions was formed, a different mechanism of asymmetric induction is apparently operative. Possible mechanisms for the induction of enantioselectivity in this case were discussed in more detail in chapter 7.

8.3 A structural and stereochemical model

A tentative structural and stereochemical model of the application of Cu-dmbpy with DNA for C–C bond forming reactions can be proposed on basis of the results described in this thesis. In order to propose a stereochemical model several aspects need to be addressed, i.e. the absolute configuration of the products, the DNA-sequence of the active site, the structure of the DNA at the active site, the binding mode of the copper complexes to DNA, and the binding geometry of the substrate to the copper complexes. Since there are multiple binding sites for Cu-dmbpy on the DNA, the discussion is focused on the most active and selective species. The following observations and interpretations have been made:

i) G-triplet sequence: The highest rate acceleration and enantioselectivity were obtained with oligonucleotides containing a G-triplet. The structure of this sequence is likely responsible for the high ee in the case of a random sequence such as salmon testes DNA.

ii) B to A distortion: CD spectroscopy revealed that the structure of the active site is markedly different from B-DNA, in the sense that it is distorted towards A-DNA (Figure 4). The difference is that the nucleobases have shifted slightly away from the central axis of the DNA.

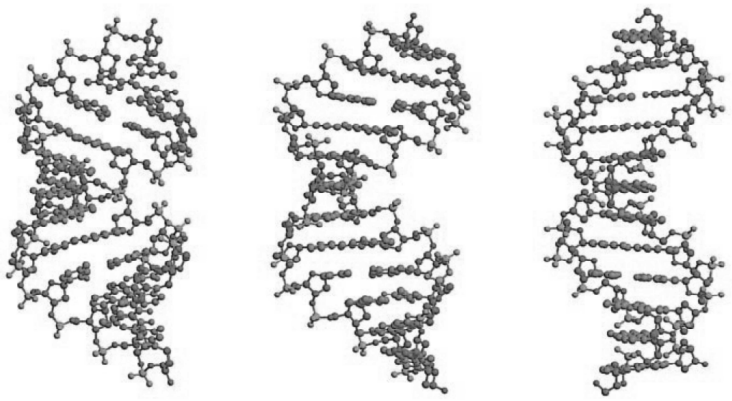

Figure 4: Crystal structures of a) A-DNA, b) d(CATGGGCCCATG)$_2$, and c) B-DNA.[14] Copyright 2000 National Academy of Sciences, U.S.A.

iii) Intercalation versus groove binding: In chapter 4, the binding mode of the copper complex to DNA is proposed to be a mixture of binding modes, including intercalation.

Moreover, it appeared that a sequence-selective change was observed in CD upon binding the metal complex, possibly caused by intercalation. Since this distortion is found only for the G-triplet-containing sequences, it might be that intercalated Cu-dmbpy dominates the reaction with respect to rate and ee over the groove-bound Cu-dmbpy.

iv) Substrate binding to Cu-dmbpy: In chapter 5 it was shown that the substrate binds Cu-dmbpy in a bidentate fashion, leading to a lowering of both the LUMO and the HOMO of the α,β-unsaturated ketone. Indirect evidence from chemical variation of the ligands in combination with EPR experiments suggested that the substrate coordinates with both the carbonyl oxygen and pyridine nitrogen in the equatorial plane of the copper(II) complex with a conformation slightly distorted from square planarity. Possibly, also an additional water molecule is present on the axial position. The conformation of the α,β-unsaturated ketone when bound to copper(II) has not yet been determined, but considering literature studies on chalcones it is likely to be s-cis.[15]

v) π-Face selectivity: The addition of the diene or nucleophiles in all C–C bond forming reactions occurred on the same π-face of the alkene, which can be extracted from the absolute configuration of the products of DNA-based asymmetric catalysis. Hence, the mechanism of stereoinduction is likely to be similar in all cases.

Based on the assumptions that the copper(II) is located on the minor groove side, and that intercalated Cu-dmbpy represents the most active complex, it is possible to construct a tentative stereochemical model that fits the experimental data (Figure 5).

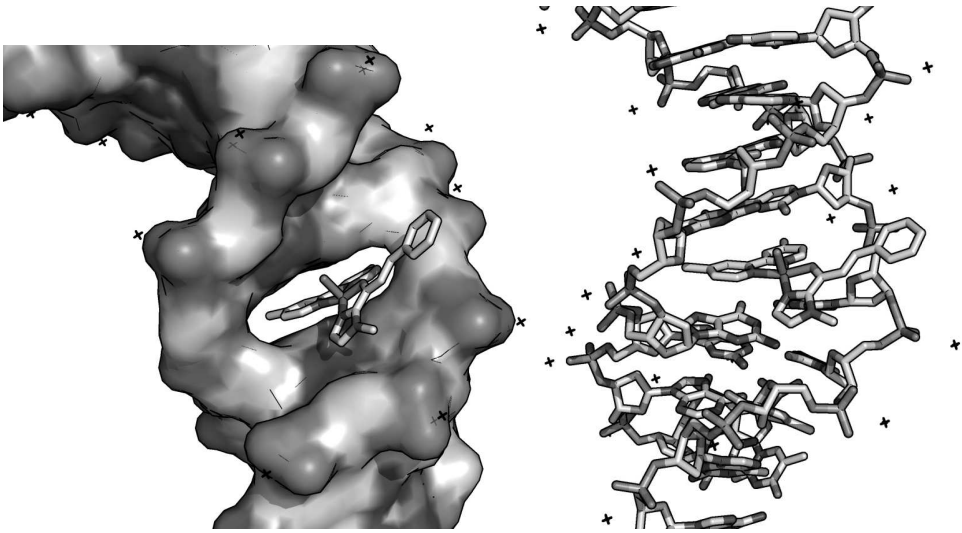

Figure 5. Tentative model of the DNA-based catalyst consisting of d(TCAGGGCCCTGA)$_2$, Cu-dmbpy, and an α,β-unsaturated-2-acyl imidazole substrate **5**.[16] Hydrogen atoms have been omitted for clarity. Counterions are depicted as crosses.

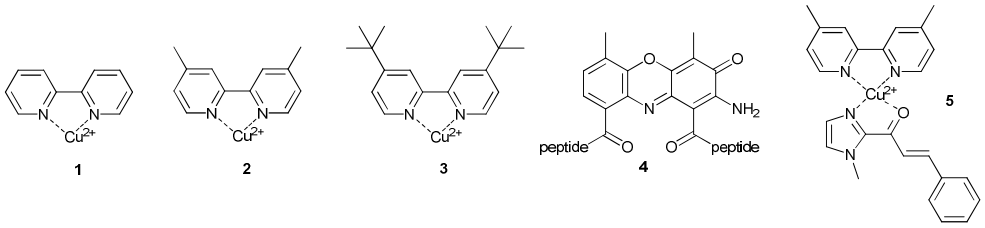

Figure 6: Structures of the copper(II) complexes of 2,2'-bipyridine (**1**), 4,4'-dimethyl-2,2'-bipyridine (**2**), and 4,4'-di-*tert*-butyl-2,2'-bipyridine (**3**). Structures of actinomycin D (**4**) and the ternary copper(II) complex of Cu-dmbpy with an α,β-unsaturated-2-acyl imidazole substrate (**5**).

In the model, the α,β-unsaturated-2-acyl imidazole is situated in the minor groove, and the close contact with the groove gives rise to ample opportunity for chiral induction. Furthermore, it shows that Cu-dmbpy can indeed fit between the nucleobases, with the methyl substituents situated in the major groove, and the copper(II) ion containing the axial water molecule situated in the minor groove. In this sense, the geometry is similar to anticancer drug actinomycin D (Figure 6), which positions two methyl substituents in the major groove, and two cyclic peptides in the minor groove.[17] Besides the 4,4'-methyl substituents, also 4,4'-t-butyl substituents can fit into the major groove in this model. The difference in the binding of the complexes in the presence and absence of these 4,4'-substituents could be that these substituents induce a more favourable geometry of intercalation by acting as "anchors" that pull the copper(II) deeper into the groove. This causes the substrate to be in closer contact with the groove, and a higher level of stereocontrol can be exerted. Furthermore interactions with the groove that enhance the reaction rate might become possible. The variation in the ee with different 4,4'-substituents on the ligand might be influenced by the balance between the ratio intercalated:groove-bound complex versus the geometry of intercalation.

As a result of steric hindrance of the 6,6'-hydrogen atoms of the bipyridine with the imidazole 4-hydrogen atom, the ternary complex is not likely to be planar. A consequence of this is that the substrate is allowed to align along the groove, i.e. parallel to the DNA backbone. The proposed mechanisms for asymmetric induction, i.e. π-face shielding, desolvation, or transition state stabilization, are all feasible in this way. In the model, the reagent approaches from the bottom face of the dienophile, the *Si*-face. Possibly, the changed geometry of the dienophile associated with the transformation of two of its sp^2 centers to sp^3 is stabilized by the shape of the groove. Although in the model the *Si*-face of the substrate is shielded, minor changes in the geometry of binding or the DNA allow shielding of the other side.

Further evidence is required that validates the model. This can be gained from a better understanding of the structure of the ternary complex, and the DNA-binding mode of the

ternary complex. Especially the sequence dependence of the DNA-binding mode of the ternary complex is crucial.

Information on the groove selectivity of binding can be extracted from paramagnetic ^{1}H-NMR, a technique employed by Sletten et al. to determine the binding sites of paramagnetic manganese(II) ions on short oligonucleotides.[18] Hence, the protons close to the metal centre show the largest paramagnetic shift. The use of model complexes based on diamagnetic metals would not provide useful information, since the copper(II) displays a unique coordination chemistry and geometry that cannot be easily compared to other metals.

Also the solid state structure of the DNA-based catalyst from X-ray crystallography would be informative, and especially the crystal structure of the ternary complex in the absence or even in the presence of DNA. However, even if a stereochemical model is available, it will represent the ground state and can give only information on shielding effects, while the enantioface selectivity is determined in the transition state. Hence, knowledge of the mechanism is required to determine the origin of the π-face selectivity. Key issues in this regard are the activation parameters, and knowledge of the various equilibriums present in order to quantify these parameters. Then, the different reactions can be compared and conclusions can be drawn.

Since the addition always occurred on the same π-face, it would be interesting to determine if the Friedel-Crafts or the Michael reaction also occur in a concerted fashion, as this would have a large influence on the structure of the activated comlex and hence, the stereoinduction. This can be determined by performing the reactions in D_2O, yielding products with a deuterium at the α-carbon. The diastereomeric outcome of such a labeling study, which can be determined with ^{1}H-NMR, in combination with a detailed kinetic study on the isotope effects would provide information if these reactions are step-wise or concerted.

8.4 Comparison with other methodologies

8.4.1 Comparison with biohybrid catalysts

A key difference between other biohybrid catalysts and the DNA-based asymmetric catalysis concept is that the biohybrid catalysts contain a single active site, while the DNA-based catalysts form many different active sites. The optimization of DNA-based asymmetric catalysts is more straightforward, since it relies only on chemical optimization. The optimization of catalysts based on proteins requires also genetic optimization, which can be troublesome since knowledge of the tertiary structure is needed. In principle, DNA-based asymmetric catalysts can also be optimized using evolution-based methodologies, which would be more facile compared to proteins since transcription and translation are not needed.

When the reaction scope of biohybrid catalysts based on DNA is compared with biohybrid catalysts based on proteins, differences and similarities can be found. For example, both approaches can be employed for C–C bond forming reactions and organometallic chemistry.[9,19-21] However, at the moment the catalytic scope can be considered complementary. The main difference is that to date the reaction scope of the biohybrid catalysts based on proteins is larger, especially in the case of redox processes. On the other hand, in the presence of DNA the Lewis-acid catalyzed C–C bond forming reactions induce higher ee's, and the enantioselective *syn*-hydration can be performed. For DNA-based asymmetric catalysis oxidation reactions might be troublesome since DNA is readily oxidized, resulting in DNA strand breaks.[22-24] However, there does exist precedent for oxidation catalysis in the presence of DNA, which was achieved by placing the catalytically active centre in G-quadruplex DNA.[25] Therefore, there is no obvious reason why asymmetric reductions or oxidations are not possible in the presence of DNA, provided that the design is appropriate. A potential issue is that the DNA bases coordinate strongly to the metal ions that are often used in catalysis,[26] but this can in principle be prevented or controlled by judicious choice of ligands and DNA structure.

8.4.2 Comparison with small-molecule catalysts

The DNA-based catalyst developed in this thesis is superior to conventional chiral catalysts for asymmetric catalysis in water as a solvent for the reactions described: generally higher ee's are obtained in water compared to existing methods for the Diels-Alder and Michael reactions.[27-29] In the case of the Friedel-Crafts reaction it is even the first catalytic asymmetric Friedel-Crafts reaction to an olefin in water. With the exception of the asymmetric conjugate addition of water, the number of highly enantioselective reactions catalyzed by the DNA-based catalyst are not yet in the range of some of the widely used existing methods for asymmetric catalysis in organic solvents. For example the pybox ligand, combined with copper(II) or scandium(III), can be employed in a wide variety of Lewis-acid catalyzed transformations with high selectivities.[30] However, the asymmetric conjugate addition of water has no equivalent with conventional catalysis. It should be noted that the DNA-based asymmetric catalysis concept has been founded only recently, and considering the pace of the advances, it is likely that other novel reactivities and selectivities can be found. Especially promising would be Lewis-acid catalyzed conjugate additions of other heteroaromatic nucleophiles, 1,3-dipolar cycloadditions, Claissen rearrangements, or hydrolysis reactions. Besides Lewis acid catalyzed reactions also new reactivities and selectivities might be found in other important types of reactions, such as hydrogenations or oxidation reactions.

8.5 DNA-based catalysis as a tool for synthesis

DNA-based asymmetric catalysis has several advantages that make it a potential useful methodology for organic synthesis:

i) DNA is an inexpensive ligand. DNA is an abundant source of chirality from Nature, and is inexpensive compared to many of the small molecule asymmetric catalysts.

ii) Water is used as a solvent. Water does not suffer from the safety hazards associated with organic solvents, and is arguably the most inexpensive solvent imaginable.

iii) The reactions are performed at 5 °C, and without a protecting atmosphere. Generally, very low reaction temperatures are employed in Lewis-acid catalyzed enantioselective transformations, in combination with a protecting atmosphere.

iv) DNA-based catalyzed reactions can easily be scaled up to mmol scale.

v) The DNA-based catalyst can be recycled. DNA is insoluble in organic solvents such as diethyl ether and ethyl acetate, and hence the water layer containing the DNA-based catalyst can be recycled after extraction of the products with an organic solvent. Indeed, in the three C–C bond forming reactions and the *syn*-hydration, the same catalyst mixture was used at least three times, without significant loss of yield or ee.

vi) Possible automated ligand libraries. An issue in asymmetric catalysis is to find the optimal catalyst for a specific reaction. A way to solve this problem is the development of automated ligand libraries. DNA offers the possibility for evolutionary optimization techniques. A drawback of using custom-made DNA instead of natural DNA are the costs associated with custom made DNA. This might be overcome by increasing the efficiency of recycling, such as coating of the specific oligonucleotides to a solid support.

vii) The imidazole moiety is readily removed from the products. This chemistry was also studied by Evans and Davies,[31,32] who showed that functional groups such as esters, carboxylic acids, ketones, and aldehydes are accessible after displacing the imidazole group. Moreover, the substrate for DNA-based asymmetric catalysis is easily synthesized in one step from commercially available compounds.

viii) The enantiomeric outcome is predictable and both enantiomers can be obtained by judicious choice of the copper(II) complex. In all C–C bond forming reactions the reactant approached the same π-face of the α,β-unsaturated-2-acyl imidazole. By influencing the coordination geometry of the substrate to the copper(II) complex, or by using copper(II) in the absence of ligand, the opposite enantiomer could be obtained.

Of course, room for improvement exists, which offers future challenges for DNA-based asymmetric catalysis:

i) The solubility of many of the reagents in water is not high. The solubility might be increased by addition of organic cosolvents, or the addition of surfactants that form micelles.

ii) The recycling has limitations so far: recycling of the catalyst mixture after a Friedel-Crafts reaction with very low catalyst loadings of 0.15 mol% copper(II) and 7 μg/ml $d(TCAGGGCCCTGA)_2$ led to a loss of all ee. This is possibly due to traces of remaining non-mixing organic solvent, which decreases the ee induced. The recycling process might be performed with lower catalyst concentrations if the oligonucleotides are attached to a solid support, and the catalyst is filtered after the reaction.

iii) An aqueous waste stream, which is more difficult to process compared to an organic waste stream. The best solution would be to be able to precipitate the product from the reaction mixture, after which the aqueous solution containing the catalyst can be recycled.

iv) The necessity of an auxiliary on the substrate for coordination to copper(II). Copper(II)-catalyzed reactions in water appear to require a bidentate coordinating substrate in order to compete with water for coordination to copper(II). Although in asymmetric catalysis bidentate-binding substrates are often used, it would be desirable if one could employ monodentate substrates such as esters, carboxylic acids, ketones, or aldehydes immediately. This might be achieved by increasing the Lewis acidity, rendering the metal bound substrate more reactive. One could think of dinuclear metal complexes, which Nature uses for phosphate hydrolyses in water.[33] On the other hand, many successful examples of catalyzed reactions of monodentate substrates in aqueous solvents are reported using scandium(III) triflate,[34] albeit in these cases high concentrations of reagents are employed in the combination with organic cosolvents. Another solution is to perform catalysis in the absence of water, which might be achieved by using cationic surfactants that precipitate DNA, after which the complex can be collected and redissolved in organic solvents.[35] Strong intercalators can bind these complexes, albeit with lower affinity.[36] Using this approach it might be possible to perform DNA-based asymmetric catalysis in pure organic solvent.

v) Finally, for some products the ee can be improved. Improvements in the structure of the ligand, e.g. different 4- and 4'-substituents, or a new ligand design could increase the enantioselectivities. It was already observed that single-stranded DNA could induce an ee of 81% in the Diels-Alder reaction, which shows that other structures than double-stranded DNA can induce high ee's as well.

8.6 Future prospects

The unprecedented reactivity pattern displayed by DNA/Cu-L paves the way for new synthetic routes to pharmalogical active compounds or natural products. Hence, in the context of organic synthesis, the future of DNA-based asymmetric catalysis is likely to be

found in small scale transformations. A key step forward would be a multistep synthesis in one pot in water as a solvent, which can be facilitated by the many new procedures that have been developed for selective transformations under mild conditions in water.[37] This might be achieved by engineering the DNA in such a way that the DNA-bound catalysts are spatially separated, and work collectively in a cascade reaction. This compares to the multi-enzyme complexes employed in Nature for non-ribosomal polyketide synthesis. These possible developments could be assisted by combinatorial or evolutionary approaches to optimize DNA sequences for a specific transformation, after which the optimized DNAs can be connected to each other to form an assembly line.

An important goal for DNA-based asymmetric catalysis is to understand the mechanism of stereocontrol and enantioselectivity, since it remains remarkable that combining a simple copper complex with a biomolecule such as DNA leads to virtual complete enantioselectivities. In this respect, Nature holds a message about the factors governing stereocontrol which is unveiled to date. Mechanistic understanding of DNA-based catalysis can be related to enzymatic catalysis, since several concepts used to understand DNA-based asymmetric catalysis are also applied to rationalize enzyme catalysis, i.e. desolvation and transition state stabilization, but possibly also the effect of enzyme dynamics on catalysis. These concepts are generally not used to explain catalysis by small molecules.

In conclusion, the unique microenvironment for catalysis created by the DNA-based catalyst described in this thesis displayed unprecedented reactivity, which will undoubtedly lead to the discovery of other new asymmetric transformations.

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